REMARKS/ARGUMENTS

Claims 29, 30, 32 and 44-61 are currently pending, claims 46-49, 52-55 and 58-61 are withdrawn from consideration as drawn to a nonelected invention, and claims 29-30, 32, 44-45, 50-51, 56-57 are rejected. Claims 29, 30 and 32 are amended herein. No new matter is added.

Examiner Interview - June 25, 2003

The applicants would like to thank the Office for taking the time to discuss the present application on June 25, 2003. The outcome of the interview provided that original claim 30 should have been placed in both Groups X and XII. Thus, prior to June 25, 2003, this Restriction option was not available to the applicants. Although the restriction has been made "Final," the applicants have not had the opportunity to traverse the requirement previously as it was unknown that claim 30 "belonged" in two separate Groups (X and XII), rather than in one Group (X) as originally presented. Nevertheless, the Office has presented one option to traverse the requirement. The applicants address the issues discussed in the interview which pertain to this aspect below. Given the history leading to this point in prosecution, the applicants respectfully request consideration of the Applicant's basis for traversal of the present restriction. Reconsideration of the Restriction Requirement is respectfully requested.

Pending Claims/Restriction

The applicants respectfully acknowledge the Office's indication that prostate, colon, breast, and lung cancers are examined in the instant application.

The present claims are directed to a method to identify a biological sample that exhibits dysregulated cellular growth or the presence of a neoplasm in a biological sample comprising determining and comparing the level of 20P2H8 gene expression in the biological sample to the level of 20P2H8 gene expression in a corresponding normal sample. As indicated throughout the specification as filed, and as is understood in the art, both mRNA and protein levels are indicative of gene expression levels. *See, e.g.*, page 45, lines 11-33 of the specification.

The present claims are directed to identifying dysregulated cellular growth or neoplasm by monitoring specific 20P2H8 gene expression. Importantly, these claims do not generically encompass an exploration for a gene then monitoring its expression. Rather, a specifically defined gene is provided and its expression can be monitored along a well established pathway known to all students of molecular biology. Although 20P2H8 protein and 20P2H8 mRNA are physically different compositions, they are inexorably tied up in the 20P2H8 gene expression pathway. As defined in the basic and well-known textbook by HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY G-7 (4th ed. 2000), "gene expression" is the "[o]verall process by which the information encoded in a gene is converted into an observable phenotype (most commonly production of a protein)." As indicated in the previously submitted Declaration by Mary Faris, Ph.D., gene expression involves the production of mRNA and protein as the gene is transcribed and translated. The present claims do not require novel methods for monitoring gene expression, and given the information provided in the present specification, it would be equally plausible to monitor 20P2H8 mRNA or 20P2H8 protein levels in monitoring 20P2H8 gene expression levels, even though such monitoring may involve different method steps. Such method steps are known in the art and, as evidenced by the structure of the present claims, are not intended to distinguish monitoring mRNA levels and protein levels as completely different inventions. Rather, monitoring 20P2H8 mRNA and 20P2H8 protein levels, as evidence of 20P2H8 gene expression levels, are separate embodiments of the presently claimed invention. In light of the present disclosure and claims, one of skill in the art could monitor 20P2H8 gene expression via methods for monitoring mRNA levels or protein levels.

Information Disclosure Statement

The Office has indicated that although a PTO-1449 form is present in the file (from a previously submitted information disclosure statement on October 2, 2001), that the references cited therein were not considered because they are missing from the file. In response, the applicants include herewith a copy of the previously filed Form 1449 and copies of the following references listed on this form: WO 00/15799, WO 00/55350, WO 00/60076, B. Birren et al. (2000), R.S. Hubert et al. (1999), and A. Kawabata et al. (2000). These references represent a selection of the references indicated as missing from the file, which were originally cited in the 1449 Form of

October 2, 2001. The remainder of the references listed on this 1449 Form from October 2, 2001, not included herewith, are all PCT publication references; the undersigned respectfully asserts that these references will be submitted for the Office's consideration in short order.

Prosecution History Summary

On December 10, 2001 the Office mailed a Restriction Requirement. In this requirement, the 43 pending claims were divided into 17 Groups. In addition, a species election was required if any of Groups I, III, X, XIV, XV, or XVI were elected.

On January 10, 2002 the applicants mailed a response to the Restriction Requirement. Therein the applicants elected Group X (claims 30, 32, 34), with traverse, regarding Groups IX and XI-XII (collectively claims 29, 31, 33), and elected the species bladder cancer. Group X recited "a method for detection of neoplasm, by measuring the expression of 20P2H8 polynucleotide, or 20P2H8 RNA level." Moreover, claims 1-28, 31, 33 and 35-43 were canceled as directed to non-elected inventions; claims 29, 30, 32 and 34 were amended in conformance with the election and traversal; and claims 44-61 were added. Traversal was based on: (1) the assertion that the invention as-claimed does not lie in any kind of novel procedure to measure the expression of the gene; the level of expression can be measured either by measuring mRNA levels or protein levels and the gene is transcribed and translated; and (2) no undue search burden was present.

On May 7, 2002 the Office mailed a communication indicating that the January 10, 2002 response was non-responsive. Although Group X was elected, there was a typo in specifying the claims in that group. On June 7, 2002, the applicants mailed an Amendment under 37 C.F.R. § 1.111 to provide clarification of Group X election.

On September 30, 2002, a second Restriction Requirement was mailed. In this restriction, the Office acknowledged the election of Group X, species bladder cancer. Moreover, Claim 29 was rejoined (presumably as Group IX, possibly as Group XI, in part) with Group X. The Office stated that the Restriction Requirement was deemed proper and therefore made final. The Office further stated that 29, 30, 32, 34, and new claims 44-45, 50-51, and 56-57 were found to "require new restriction." However, this requirement for new restriction was not elaborated by the Office. In addition, there *appeared* to be a species election to one of the tissues in claim 34.

The Office further indicated that claims 29, 30, 32, 34, 44-45, 50-51, 56-57 were "examined only to the extent of a method for identifying bladder cancer comprising detection of mRNAs." The Office refused to examine a selection of the newly added claims as "independent or distinct from the invention originally claimed." The basis for this decision was that "[n]ewly submitted claims 44-61 are directed to an invention that is independent or distinct from the invention originally claimed." Further, the Office asserted that "[t]he two methods differ in method steps and reagents used, since the structure of mRNAs is different from that of the encoded protein." The Office asserted that "[s]ince applicant has elected Group X, a method for identifying bladder cancer comprising detection [sic] the levels of mRNAs of 20P2H8 gene, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits." However, the Office did not mention that claim 30 was *also* directed to measuring expression of 20P2H8 polynucleotide (i.e., including both mRNA and protein expression); this aspect of claim 30 currently appears to be omitted by the Office. Importantly, the applicants had not elected "detecting levels of mRNA of 20P2H8," as this option had not previously been presented. Claim 30 only existed in Group X, and was not split into two or more Groups at the time that election was required by the Office.

On October 31, 2002, the applicants mailed a response. Therein claim 34 was canceled and the species election thereof was rendered moot. The applicants submitted that the restriction of claims 29, 30, 32, 34, 44-45, 50-51, and 56-57 was unclear. The applicants further submitted that production of mRNA is predictive of the corresponding protein; 20P2H8 gene expression can be monitored by measuring mRNA levels or protein levels. An expert Declaration of Dr. Challita-Eid was provided to support this position. In addition, the applicants submitted that the claimed invention does not lie in any kind of novel procedure to measure the expression of the gene.

On January 24, 2003, the Office mailed a Communication. In this Communication the office indicated that a species election was required, but that the applicants did not elect a biological sample species. Moreover, the Office asserted that the issue was *not* rendered moot via the cancellation of claim 34. In this Communication the Office did not acknowledge the previous election of bladder cancer, nor the expert Declaration.

On February 24, 2003, the applicants mailed a response to the Office Communication. Therein the applicants submitted that they did not understand the January 2003 request for further

species election. The applicants questioned the need for a *further* species election, as the subject "biological samples" are derived from bladder tissue, and the "species" bladder cancer was previously elected. Applicants further submitted that they were entitled to a response on the evidence submitted (i.e., the Declaration), and that all pending claims should be examined together.

On March 23, 2003, the Office mailed the First Action on the merits. In this Action, the expert Declaration was "acknowledged," yet determined not to be persuasive. Despite the Declaration, the Office did to examine the claims to the extent that they read on gene expression as claimed by applicants (i.e., including the detection of 20P2H8 mRNA or protein). The Restriction Requirement was again made final. The Office stated "whether there is sufficient correlation between mRNA production and protein production, this issue is an enablement issue, and is not considered here." Moreover, the species prostate, colon, colorectal, breast and lung cancers are rejoined with species bladder cancer. Dysregulated growth, neoplasm and several cancers were withdrawn as directed to non-elected "species."

Objections to the Figures/Specification

The Office has objected to Figures 2 and 3 as not being clear which of the bands represents 20P2H8 mRNA. The basis for this objection provided by the Office is that the Figures purportedly contain multiple bands and no molecular size standards. The applicants thank the Office for the close review of the data presented and provide replacement Figures for Figures 2A-2C herewith to address the present objection to the Figure 2. Size standards are included in these replacement figures. Figure 3, as previously provided, contains the requested size standards. Thus, the applicants believe that the objection provided by the Office does not apply to current Figure 3. Moreover, the objection to Figure 3 relates to form not necessary for further consideration of the present claims. Thus, if the Office maintains the present objection to Figure 3, the applicants respectfully request that the Office hold this requirement in abeyance until allowable subject matter in this application is indicated. *See* 37 C.F.R. § 1.111(b).

Objections to the Claims

The Office has objected to pending claims 29-30, 32, 44, 50 and 56 as drawn to a nonelected invention. Respectfully, as separate Groups/species encompassing either detecting mRNA or protein expression as indicative of 20P2H8 gene expression were not previously provided by the Office, neither encompasses a nonelected Group/species. The present traversal of this requirement is included hereinabove. If, however, the Office maintains the present restriction/election between detecting mRNA and protein levels, the applicants respectfully request that the Office examine the claims to the extent that they read on the Group/species asserted by the Office as previously elected.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office has rejected claims 29-30, 32, 44-45, 50-51 and 56-57 under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. The Office has specifically indicated that claims 29-30, 32, 44-45, 50-51 and 56-57 are indefinite for the use of the language "20P2H8 gene" as the "sole means of identifying the claimed gene." The applicants have amended the subject claims in accordance with the Offices rejection to include a more definite description of the subject gene. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

The Office has rejected claims 29-30, 32, 44-45, 50-51 and 56-57 as purportedly not enabled. The Office has indicated that the specification does not provide sufficient information to one of skill in the art to make and/or use the claimed invention. The Office has specifically indicated that there is a discrepancy in the test results such that RT-PCT data does not provide differential expression in prostate tumor tissue, whereas Northern Blot data does indicate differential expression.

Respectfully, as indicated in Figure 2, the cDNA was analyzed by RT-PCR using 25x and 30x amplification. Thus, due to the amplification, the results are no longer quantitative, but only qualitative. The Northern analysis, however, is a quantitative experiment. Thus, differential expression is not definitively shown in Figure 2, but differential expression is clearly present in the

Northern data depicted in Figure 3, for example. Accordingly, the applicants assert that the present data do not indicate a discrepancy in test results.

As for the probe used in the generation of the Northern blot data, the applicants respectfully direct the Examiner's attention to the Examples section in the specification. In particular, Examples 1-3 discuss the generation and isolation of the cDNA probe utilized in Northern analyses. *See, e.g.*, pages 61-64. This probe is the PCR product of the primers identified in the specification. *See, e.g.*, pages 62-64.

Rejections Under 35 U.S.C. § 112, First Paragraph, Scope

The Office has rejected claims 29-30, 32, 44-45, 50-51 and 56-57 as encompassing a scope that is purportedly not enabled by the specification. The Office has indicated that the specification does not provide sufficient information to one of skill in the art to make and/or use the claimed invention.

The Office has specifically indicated that the claims encompass an alteration in the level of gene expression in a test sample compared with a normal sample. The Office asserts that "alteration" could mean either increase or decrease in expression levels. However, the Office has cautioned that the specification only teaches an increase in gene expression levels in a test sample versus a normal sample as indicative of cancer. In light of the present claim amendments, the applicants respectfully request withdrawal of this rejection. Respectfully, the applicants assert that this rejection is not properly applied to claims 32, 56 and 57. The applicants assert that these claims do not recite the disputed language and thus fall outside of this rejection.

The Office has further specifically indicated one could not detect prostate, colon, breast, lung or bladder cancer via an alteration in the expression level of the 20P2H8 gene in "any" sample. It appears that the Office is requiring more specificity regarding sample source materials. In response, the applicants assert that defined gene expression is currently claimed, which is not limited to expression within certain tissues. Certainly one of skill in the art would understand that given the tools provided in the present disclosure, it is possible to measure the expression of the claimed gene in any of a number of tissues. The present disclosure indicates that the claimed gene has been

shown to be expressed or overexpressed in certain tissue types and disease states. The present claim amendments address the Office's concern in this regard. Withdrawal is respectfully requested.

Rejections Under 35 U.S.C. § 102

The Office has rejected claims 29-30, 32, 44-45, 50-51 and 56-57 under 35 U.S.C. § 102(a) as purportedly anticipated by WO 99/38972. The Office has specifically indicated that WO 99/38972 teaches a sequence (listed as SEQ ID NO: 3624 in WO 99/38972) that is 98% similar to the claimed 20P2H8 gene (SEQ ID NO: 1), from nucleotide 1 to 599. The Office further asserts that "WO 99/38972-A2 further teaches detecting differentially expressed gene correlated with the cancerous state of mammalian cells, such as colorectal cancer, breast cancer and lung cancer, comprising detecting the polynucleotide disclosed."

Respectfully the claimed gene contains an open reading frame starting at nucleotide residue 453 in SEQ ID NO: 1, having a putative Kosak sequence beginning at nucleotide residue 447. The claimed gene contains a full length of 3600 base pairs and encodes a 517 amino acid open reading frame. The sequence cited by the Office purportedly merely spans from nucleotide 1-599 of the claimed gene. Thus, the sequence cited by the Office here only encompasses only about 9% of the open reading frame of the claimed gene. There is no indication that the sequence cited by the Office would be detected under the currently claimed methods. More importantly, it appears that the presently claimed gene, and its corresponding expression, would not be detected by the sequence disclosed in WO 99/38972. The present claim amendments fully support this assertion. Accordingly, the applicants assert that the sequence cited by the Office is not properly applied to the present claims. Withdrawal of this rejection as it pertains to the pending claims is respectfully requested.

The Office has rejected claims 29-30, 32, 44-45, 50-51 and 56-57 under 35 U.S.C. § 102(e) as purportedly anticipated by U.S. Patent No. 6,262,333 (hereinafter the "'333 patent"). The Office has specifically indicated that the '333 patent teaches a sequence (listed as SEQ ID NO: 380 in the '333 patent) that is 96% similar to the claimed 20P2H8 gene (SEQ ID NO: 1), from nucleotide 1388 to 1726. The Office further asserts that "SEQ ID NO:380 is overexpressed in cancer tissue. US 6,262,333 further teaches a method for detecting cancer, using the disclosed polynucleotide."

Respectfully, the claimed gene contains a full length of 3600 base pairs and encodes a 517 amino acid open reading frame starting at nucleotide residue 453 in SEQ ID NO: 1. The sequence cited by the Office purportedly merely spans from nucleotide 1388-1726 of the claimed gene. Thus, the sequence cited by the Office here only encompasses only about 21% of the open reading frame of the claimed gene. There is no indication that the sequence cited by the Office would be detected under the currently claimed methods. More importantly, it appears that the presently claimed gene, and its corresponding expression, would not be detected by the sequence disclosed in the '333 patent. The present claim amendments fully support this assertion. Accordingly, the applicants assert that the sequence cited by the Office is not properly applied to the present claims. Withdrawal of this rejection as it pertains the pending claims is respectfully requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants' petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **511582002100**.

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Respectfully submitted,

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Expression of 20P2H8 in LAPC xenografts and restricted normal tissues

Fig.2A

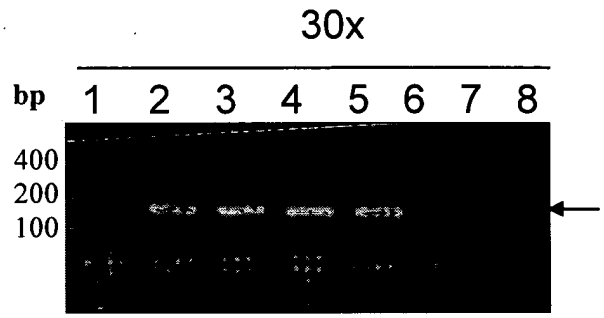
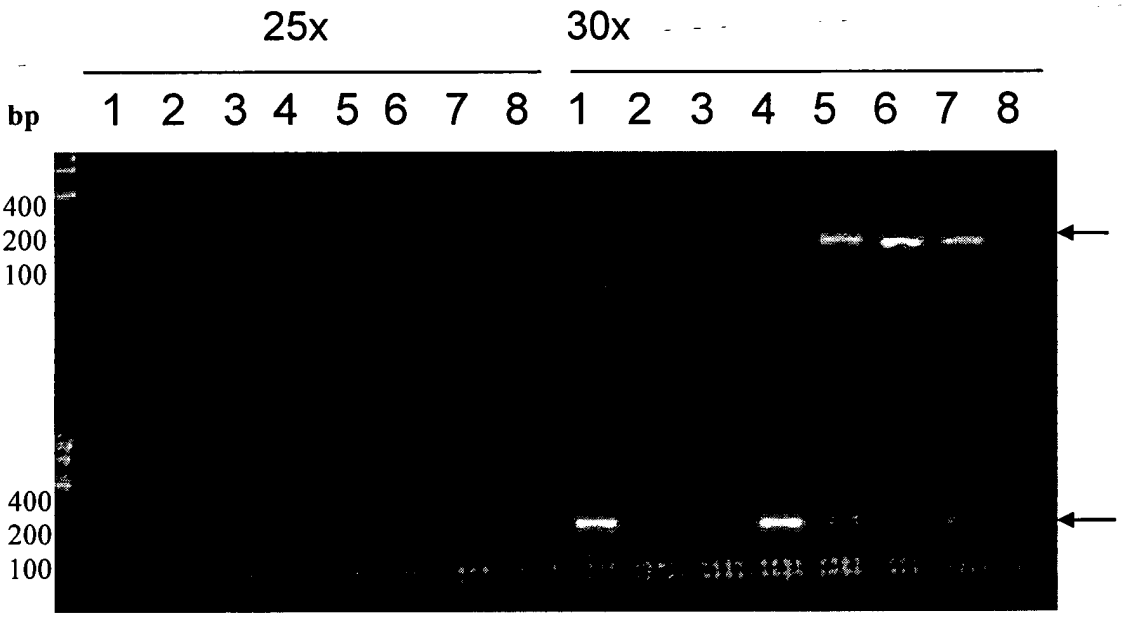


Fig.2B

Fig.2C



To add to legend of Figure 2:

The primers used for the RT-PCR are specific for 20P2H8 and are as follows: 5'-TCTTGAAACCTCCAGACACAAGAA-3' and 5'-AAGTTACGATTTGGCTTCACTGG-3'. The 20P2H8 PCR product is expected to be of 162 base pairs as marked by an arrow.

Reg. rule compliance.